REMARKS

Claim 1 was submitted in a Preliminary Amendment filed August 28, 2002. Claims 2-60 are canceled. New claims 61-71 are added herein. Applicant respectfully requests that new claims 61-71 be entered. Therefore, claims 1 and 61-71 are currently pending. Reconsideration in view of the amendments above and the remarks below is respectfully requested.

Support for new claim 61 can be found, for example, in the originally filed claim 7. Support for new claim 62 can be found, for example, in the originally filed claim 16. Support for new claim 63 can be found, for example, in the originally filed claim 17. Support for new claims 64-67 can be found in the specification, for example, at page 46, lines 16-28. Support for new claims 68-71 can be found in the specification, for example, at page 8, lines 1-4 and page 79, lines 9-12.

Applicant respectfully submits that the present Response places the pending claims into the properly elected restriction group set forth by a Preliminary Amendment filed on August 28, 2002.

The remarks which follow are directed to the Office Action mailed June 18, 2003 (hereinafter the "Action") and are made in order to assure that a complete response is made to the Office Communication mailed April 20, 2004.

A. Rejection under 35 U.S.C. § 112, First Paragraph

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for a method of specifically activating cytotoxic T lymphocytes (CTLs) *in vivo* in a subject

having a tumor expressing HER-2/Neu, wherein said CTLs could target or kill tumor cells expressing HER-2/Neu *in vivo*. The present rejection is respectfully traversed for reasons of record and the reasons discussed below.

Applicant respectfully submits that the Examiner has misconstrued the test of enablement by requiring a working example be provided that demonstrates a result that immunizing an animal with the claimed polypeptide of SEQ ID NO:10 results in the targeting or killing of tumor cells expressing Her-2/Neu *in vivo*.

The test of enablement, however, is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (see, e.g., *In re Wands*, 858 F.2d at 737,8 USPQ2d at 1404 (Fed. Cir. 1988)). There is no requirement in the test of enablement that a working example demonstrating a desired result be provided in the specification. An applicant need not have actually reduced the invention to practice prior to filing. *In Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." *In Gould v. Quigg* 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).

In regard to the enablement requirement, there can be no question that it is met, for an analysis of the Wands factors reveals that the claimed invention does not require undue experimentation for one skilled in the art to make and use the

claimed invention as discussed below.

(1) The Breadth of the Claims and Nature of the Invention

The claims, as amended, are limited to a method of activating CTLs *in vivo*, wherein the CTLs specifically target malignant cells that express a Her-2/Neu protein *in vivo*, comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10. Thus, the claimed invention requires immunization with a polypeptide which is fully disclosed in the specification including a disclosure of its sequence (SEQ ID NO:10). The specification further discloses a working example of the step of immunizing an animal with the polypeptide of SEQ ID NO:10 (see, e.g., page 86, lines 25-30 which references, e.g., page 79, lines 7-12)

(2) The State of the Art and the Level of Skill in the Art

The state of the art at the time the application was filed was highly developed such that the step of immunizing an animal with a polypeptide was routine in the art. The level of skill of one of ordinary skill in the art, at the time the application was filed, was high, as apparent from the fact that many practitioners have attained a post-graduate level of education and/or years of experience in the art.

(3) The Level of Predictability in the Art

The Examiner asserts at page 3, first paragraph, of the Action that it is, "unpredictable that one can specifically target or kill malignant cells that express Her-2/neu in an animal having a tumor burden that express Her-2/neu, due to self-tolerance as taught by Sherman et al. of record" (Sherman et al.

Critical Review in Immunology 18 (1-2): 47-54).

Sherman et al. states that a, "potential barrier in the identification of T-cell epitopes derived from these proteins [tumor associated proteins] and presented by tumor cells is the fact that these proteins are also expressed at low levels in some normal tissues, and therefore, self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity" (emphasis added).

Thus, Sherman et al. does not teach that self-tolerance will occur. Also, Sherman et al. does not teach that self-tolerance will occur for every peptide used as an immunogen. For example, Sherman et al. discloses that immunization of $A2K^b$ mice with a recombinant strain of vaccinia virus containing a minigene encoding the sequence of the hu p53.149 peptide prevented growth of EL4 $A2K^b$ p53 tumor cells. Thus, self-tolerance does not eliminate the CTL response for all immunogens expressed at low levels by normal tissues at evidenced by Sherman et al.

Furthermore, as discussed immediately below, immunization of $A2.1/K^b$ transgenic mice with the claimed Her-2/Neu polypeptide of SEQ ID NO:10 results in the specific activation of CTLs *in vivo*, even though the mice express Her-2/Neu at low levels in normal tissues (Sherman et al., for example, teaches that Her-2/Neu is expressed at low levels in normal tissues at page 47, column 2, lines 4-16). The specification teaches that immunization of $A2.1/K^b$ transgenic mice (see, e.g., page 86, lines 25-30 which references, e.g., page 79, lines 7-12) specifically activates CTLs *in vivo* wherein the activated CTLs from the immunized mice specifically target malignant cells that express the Her-2/Neu protein *in vitro* (see, e.g., page 86, line 25 through page 89, line 16 which references page 79, lines 7 through page 80, line

12).

Thus, even though the A2.1/K^b transgenic mice express low levels of Her-2/Neu, one of ordinary skill in the art would not doubt that immunization with the Her-2/Neu polypeptide of SEQ ID NO:10 still results in specific activation of CTLs *in vivo*. The specific activation of CTLs *in vivo* in an animal model wherein Her-2/Neu is expressed at low levels, and wherein the activated CTLs target Her-2/Neu tumors *in vitro* demonstrates that self-tolerance does not eliminate the activated CTLs response to the immunogen SEQ ID NO:10 *in vivo* through self-tolerance. Therefore, the Examiner's assertion that it is allegedly unpredictable that one can specifically activate CTLs which target Her-2/Neu expressing tumors due to self-tolerance as taught by Sherman et al., is without merit and should be withdrawn because the specification demonstrates that, in fact, CTLs were activated *in vivo* in an animal model that expresses low levels of Her-2/Neu by immunization of the animal with the polypeptide of SEQ ID NO:10.

The Examiner next asserts at page 3, first paragraph, of the Action, that, "unless tested, it is unpredictable that mice having tumors that express Her/Neu would produce CTLs specific for SEQ ID NO:10 with high affinity". Applicant respectfully submits that the claims do not recite an element that immunization with SEQ ID NO:10 "would produce CTLs specific for SEQ ID NO:10 with high affinity". Thus, the present assertion should be withdrawn because the claims do not recite the asserted element.

The Examiner next asserts, from the bottom of page 3 through the middle of page 4 of the Action, that one could not extrapolate the *in vitro* tumor cell killing with *in vivo* tumor

cell killing because 1) allegedly the characteristics of tumor cell lines *in vitro* are different as compared to primary tumor cells (Freshney et al, Dermer et al, or record) and the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, could be subsequently lost due to an autochthonous immune response (Cheever et al, of record, column 9, first paragraph), 2) allegedly the *in vitro* and *in vivo* environments are different, and 3) allegedly conditions for targeting tumor cells are different as the tumor cells *in vitro* are continuously exposed to CTLs and cytokines.

Applicants respectfully submit that tumor cell lines are a suitable model system for the correlation of *in vitro* results to *in vivo* conclusions (see, e.g., *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Thus, even if the disclosed example of an *in vitro* testing system is different from an *in vivo* application (i.e., targeting malignant cells that express a Her-2/Neu protein *in vivo*), this difference in and of itself is not sufficient to establish a prima facie case of lack of enablement unless there is reason to doubt the objective truth of the statements contained in the application which must be relied on for enabling support (see, e.g., In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)).

As discussed above, the Examiner asserts that the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, <u>could</u> be subsequently lost due to an autochthonous immune response (Cheever et al, of record, column 9, first paragraph) (emphasis added). However, the Examiner fails to provide evidence

that an autochthonous immune response does occur, or that the response occurs in all individuals and tumors. Furthermore, the claims, as amended, specifically recite the element that the activated CTLs target malignant cells that express a Her-2/Neu protein *in vivo*. Thus, the invention is not directed to cells that do not express a Her-2/Neu protein; therefore, the present rejection is without merit and should be withdrawn.

Also as discussed above, the Examiner asserts that the conditions for targeting tumor cells (*in vitro* versus *in vivo*) are different as the tumor cells *in vitro* are allegedly continuously exposed to CTLs and cytokines. However, the Examiner never provides evidence that this alleged difference of continuous exposure to CTLs and cytokines renders the *in vitro* targeting of malignant cells that express a Her-2/Neu protein an irrelevant model system, or working example, for the targeting of malignant cells that express a Her-2/Neu protein *in vivo*. For example, the Examiner never provides evidence that tumor cells *in vivo* are not also continuously exposed to CTLs and cytokines after immunization with the polypeptide of SEQ ID NO:10.

Next, the Examiner asserts at page 4 of the Action that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells. As discussed above, Applicant respectfully submits that the claims recite the element that the activated CTLs specifically target malignant cells that express a Her-2/Neu protein. Thus, the claimed invention, as amended, is directed to those tumors that do express Her-2/Neu protein *in vivo*. Therefore, the present rejection is without merit and should be withdrawn.

(4) The Amount of Direction Provided by the Inventor.

As discussed below, Applicant respectfully submits that the amount of direction provided by the specification was enabling. The specification discloses how to make the polypeptide of SEQ ID NO:10 (see, e.g., page 84, lines 25-35); discloses how to immunize an animal with the polypeptide of SEQ ID NO:10 (see, e.g., page 86, lines 25-30 which references, e.g., page 79, lines 7-12); discloses that CTLs were activated by the immunization; and discloses that, when collected, the activated CTLs specifically target malignant cells that express a Her-2/Neu protein *in vitro* (see, e.g., page 86, line 25 through page 89, line 16 which references page 79, lines 7 through page 80, line 12). The level of direction provided in the specification was enabling at the time of filing because one of ordinary skill in the art was able to make and use the claimed invention without undue experimentation.

(5) The Existence of Working Examples.

Applicant respectfully submits that the testing of the activated CTLs *in vitro* constitutes a working example of the claimed invention as discussed below. MPEP 8r1 2164.02 states that, "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention". The use of tumor cell lines was an accepted model system for testing of anti-cancer agents commonly used by the National Cancer Institute at the time the application was filed (see, e.g., *In re Brana*). Furthermore, there is no requirement that a working example be provided in the specification (see, e.g., MPEP 8r1 2164.02. An applicant need not have actually

reduced the invention to practice prior to filing. *In Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987).

(6) The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure.

Based upon the disclosure, and the knowledge present in the art, Applicant submits that one of ordinary skill in the art would easily have been able to immunize an animal having malignant cells that express a Her-2/Neu protein *in vivo* with the polypeptide of SEQ ID NO:10 without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (see, e.g., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)). In the present case, it is respectfully submitted, that the experimentation needed to immunize an animal having malignant cells that express a Her-2/Neu protein *in vivo* with the polypeptide of SEQ ID NO:10 does not even rise to the level of being complex because the specification discloses how to immunize an animal with the polypeptide of SEQ ID NO:10. Therefore, the present rejection should be withdrawn because, in view of the knowledge in the art, Applicant discloses how to make and use the claimed invention without undue experimentation.

B. Rejection under 35 U.S.C. § 103

Claim 1 is rejected under 35 U.S.C. § 103 as allegedly being obvious over Grey et al., of record (WO 94/20127), in view of Cheever et al., of record (5,726,023); Englemen et al., of record

(4,950,598; and Yoshino, et al. 1994, J Immunol, 152(5):2393-2400, for reasons of record as set forth in paper No:21. It is noted by the Examiner at page 5 of the Action that the present rejection only concerns activation of CTLs in mice without tumor burden. Applicant respectfully traverses the present rejection for reasons of record. However, in view of the amendment to claim 1 above, Applicant respectfully submits that the present rejection is moot and; therefore, should be withdrawn.

CONCLUSION

Claims 1 and 61-71 are pending in the present application and conform to the proper restriction group as set forth in the Preliminary Amendment mailed August 28, 2002. Applicant believes that claims 1 and 61-71 are in condition for allowance and earnestly solicits an early notification of allowance from the Examiner.

The Commissioner is hereby authorized to charge Deposit Account No. 19-0962, should any additional fees be required in this application.

Respectfully submitted,

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Date

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